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(An Undergraduate Publication)

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Volume VIII TORONTO, NOVEMBER, 1930 Number 1

EDITORIAL.

With this number, the Journal enters upon its eighth year. Thanks to the support given it each year by over ninety per cent. of the undergraduate body, it is in excellent health. Provided that this support is continued, it has every reason to look forward to a year of increased vigor and usefulness.

In this number we present a comprehensive account by Dr. Ryerson of an event of great interest to the undergraduates, the opening of the Banting Institute.

Particularly timely is the article by Mr. J. C. Thomas which apears in this number on the history of the attempts at extraction and production of insulin. Mr. Thomas' article presents two other features of more than passing interest—the story of how a scientific discovery of the first magnitude was managed for the public benefit, and an example of the steps in the mass production of a biological substance.

The article by Mr. H. N. Taube on "Diverticulosis and Diverticulitis" is recommended as an exhaustive review of the literature on this subject to the present time. This is a condition which we will hear more about as knowledge of its frequency and of methods of diagnosis becomes widespread in the profession.

The synopsis of Dr. George Young's address on "Disorders of the Thyroid" indicates a very practical point of view and one that is new to many of us.

Mr. H. R. Brillinger's article on "Surgical Tuberculosis of Kidney," presents a well balanced discussion of the most recent knowledge on the pathology, diagnosis and treatment of this condition.

Mr. R. B. Kerr's article, "The Control of Erythrocyte Formation," and Mr. D. Telford's, on the lymphatic system, will be of particular interest to the junior years. We hope to publish in an early issue an article complementary to Mr. Telford's on the functions of the lymphatic system, a subject that is very inadequately treated in many of our text books.

PROFESSOR J. P. McMURRICH.

It was with great regret that the student body received the news of the retirement of Professor J. P. McMurrich from the chair of Anatomy, which he has occupied with great distinction since 1907.

A graduate of University of Michigan, his picture is still to be seen in the medical college at Ann Arbor. Dark hair, trimmed Van Dyke, sharp aesthetic features, prophesied a brilliant scientific future. Later he appears as an expert anatomist particularly in the study of histology; as an adviser in international biological problems which took him over most of Canada and the United States, and to Australia, where the Atlantic Salmon grew from experimental proportions to those of a large fish industry; and ultimately as a very able organizer of teaching staffs and as a mellow Dean of Graduate Studies.

Reading has been one of his great hobbies, particularly reading with a scientific flavor; so it is natural that he should carry over his vigor into the study of Science and Civilization.

It has been fortunate that his academic interests have made it possible for students of all years in medicine and for graduates of other faculties, to enjoy his teaching, his personality, and his wisdom. It is unfortunate that succeeding generations will miss this pleasure—and the red cravat.

PROFESSOR J. C. B. GRANT.

It gives us great pleasure to welcome, on behalf of undergraduates, Professor J. C. B. Grant to the Faculty of Medicine.

Professor Grant graduated from Edinburgh in 1908 as an M.B. and gold medalist in pathology. Since then he has acquired further academic honors, M.D., Ch.B. with honors, and F.R.C.S. (Edinburgh). After graduation his interests turned definitely to the study of Anatomy, in which he has been an international figure, as editor of Gray's Anatomy, and as a teacher at Edinburgh, Durham and Manitoba Universities. Ingenious methods of teaching, including specially constructed models and extensive use of X-Ray plates, have given his students not only a clear conception of anatomy, but a great deal of admiration for the man. Recent graduates of Manitoba frequently refer to their grip on the study of anatomy from the "outside in" and to the ease with which their knowledge can be applied in medical practice. We leave it to the younger anatomists in the faculty to substantiate his thoroughness and ingenuity. Furthermore, Professor Grant had a distinguished career in the war, and was decorated for his services. His methods of teaching and his personality will undoubtedly evoke here the feeling of admiration which he has aroused in his students in other universities.

The Opening of the Banting Institute.

By Dr. E. Stanley Ryerson.

The Banting Institute of the University of Toronto was formally opened on Tuesday. September 16th, 1930, by Lord Moynihan of Leeds. The programme of the proceedings included the opening ceremony in Convocation Hall, inspection of the buildings, a special convocation for the conferring of Honorary Degrees, a Reception and Garden Party, and an official dinner.

At the formal opening the Chairman of the Board of Governors, the Hon. and Rev. H. J. Cody, described how the Banting Institute had come to be built with funds amounting to $935,000, secured from the Provincial Government of Ontario, the University of Toronto and the Toronto General Hospital for replacement of the present Pathological Building. Ten years ago, the Faculty of Medicine drew up an outline of the additional buildings that would be required to provide adequate facilities for teaching and research purposes, and with the completion of the Banting Institute, the ideals set forth at this time had now reached their consummation.

The building is located on the north side of College Street opposite the Toronto General Hospital, with which it is connected by an underground tunnel. The structure is reinforced concrete faced with red brick and trimmed with Indiana limestone, the architecture being of the Georgian type. There are five stories above a basement and subbasement, with passenger and freight elevators. The main floor is occupied largely by the department of pathology with a group of five rooms for routine Pathological examination of material from the General Hospital and with a large departmental library.

In the east wing is situated the lecture theatre for 200 students in which provision is made for lantern projection or moving picture demonstration. The department of Bacteriology occupies the second floor with a large student laboratory for 150 students, which will be utilized for both bacteriology and pathological histology. The third floor is assigned to the clinical departments of Medicine, Surgery, Obstetrics and Gynaecology and to a library of books and journals. In this is to be hung the portarit of Lord Lister, which Lord Moynihan will unveil later in the morning. On a mezzanine floor between the third and fourth floors, is a students' laboratory for the teaching of pathological chemistry and clinical microscopy, which will accommodate about 150 students. On the fourth floor, the laboratories of the department of pathological chemistry are located. The facilities for the various workers under the Banting and Best Chair of Medical Research are situated on the fifth floor, with complete operating rooms and their accessories for Experimental Surgery in the west wing. Two rooms are used by the Art Service of the Faculty, where drawings, paintings and wax models are prepared by the Artist.

Animal quarters for the various departments in the building are located on the roof of the west wing. The basement floor is devoted to a large number of small museum rooms, in each of which are shelved the gross pathological specimens of the various body systems. The autopsy room with seats for 120 students is in the east wing, where the morgue is also located.

Following this introductory address, Dean Primrose introduced the University representatives, who advanced as their name and university were announced and shook hands with the Chancellor and the Chairman of the Board

Lord Moynihan then delivered the

formal address (which will be published in full) and declared the building open, after which he unveiled the portrait of Lord Lister, which was presented to the University by the late Dr. F. LeM. Grasett, formerly Emeritus Professor of Surgery in this University, and Dr. H. St. G. Baldwin, both of whom were former house-surgeons of Lister at Edinburgh.

At the end of the proceedings, everyone repaired to the Banting Institute on College Street, where Lord Moynihan unlocked the door and declared the building open for inspection. Registration of guests was carried out in the main corridor with the signature of names in the Official Register. The purpose for which each room was to be used was designated by a placard over the door, enabling guests to inspect and understand the various types of teaching and research facilities provided for the building.

At one o'clock, the members of the Faculty Council entertained at a Buffet luncheon in the bacteriological laboratory, the representatives from other Universities, the members of "Tour C" of the British Medical Association on their way back from the annual meeting of the Association in Winnipeg, and a number of out of town graduates and guests.

In th afternoon a Special Convocation was held in Convocation Hall for the conferring of honorary degrees. In presenting for the degree of LL.D. the Rt. Hon. Lord Moynihan, K.C.M.G., C.B., M.D., M.S., P.R.C.S., LL.D. Leeds, the Dean of the Faculty of Medicine, Dr. A. Primrose, referred to the distinguished services rendered by His Lordship in war and in peace. "Lord Moynihan," he said, "holds the rank of honorary major-general of the British army, and during the war acted as consulting surgeon for the forces overseas. He was particularly noted for his treatment of heart and lung injuries suffered by soldiers. He himself is the son of Captain Moynihan, V.C."

"In addition to his post as President of the Royal College of Surgeons, he is an emeritus professor of Surgery in the University of Leeds and consulting surgeon to the Leeds General Infirmary. He already holds degrees from the Universities of Leeds, Edinburgh, Bristol, Ghent, Dublin and Belfast."

"Rcognized the whole world over as one of the most outstanding surgeons, His Lordship's books constituted the best guide for the practice of surgery in many languages."

Thomas Stephen Cullen, M.B., professor of clinical gynaecology of Johns Hopkins University, was presented by Professor W. B. Hendry, head of the Department of Obstearics and Gynaecology in this University. He pointed out that Dr. Cullen was a graduate in medicine of the University of Toronto, who was a silver medallist in 1892. He said it was principally for his work on cancer and the fact that he was the first one in the United States to inaugurate the National Committee on Cancer Research that Dr. Cullen was being presented for the degree of LL.D.

Charles Seward Blackwell, Chairman of the Board of Trustees of the Toronto General Hospital, was presented for the same degree by Sir Joseph Flavelle, Bart., who declared that Mr. Blackwell had brought to his duties marked business ability and sympathy and had rendered notable constructive service to the people of the city and the Province. He spoke of his keen interest in the project of the Banting Institute and the material assistance afforded by it to the hospital.

The degree of Doctor of Science D.Sc., was conferred upon Davidson Black, M.A., M.B., in absentia. His name was presented by Professor J. P. McMurrich, who has recently resigned as Professor of Antomy and Dean of the Graduate School in the University. Professor McMurrich referred to Dr. Black as a graduate of the University, who had attained world renown by his anthropological discoveries. His study of anthropology in Chou Kou Tien in

far-off Northern China, had culminated in his recent find of the sinanthropus. He has held the position of professor of Anatomy in Peiping Union Medical College.

The Chancellor then said that the audience would appreciate hearing some remarks from Lord Moynihan.

Lord Moynihan expressed his appreciation of the honour which had just been conferred upon him. He paid a high tribute to the Medical School of the University of Toronto, declaring that the school here stood very high among the medical schools of the world to-day. It attained this position by virtue of its splendid team work and the willing and substantial aid of the lay district which it served. It was appropriate, he thought, that one of the greatest medical discoveries since the day of Lord Lister should have its home here.

As President of the Royal College of Surgeons he referred to the conducting of the Primary examinations for the Fellowship in Toronto and Montreal in the last two years as a means of obviating the expense to candidates of two trips to the Old Country, a thing which he never could have afforded when he was a medical student. He outlined the plans which were being forwarded in England for the accommodation of post-graduate students from the Dominions, noting that a recent grant had been made by the Government for a post-graduate teaching college, which is to be opened in Hammersmith, London. He also expressed the hope that the plan of establishing a "Canada House" in Bloomsbury would be consumated so that "students from the Dominion would feel that it is their own little bit of London."

In a stirring peroration, he paid a glowing tribute to Dr. Banting and the benefit he had conferred upon humanity by his discovery.

Dr. T. S. Cullen, in responding, recalled many interesting reminiscences of the early days of the Medical School of the University of Toronto.

Mr. C. S. Blackwell said he wanted to thank the Chancellor and Senate for the great honour they had done him. He felt that they wanted to pay recognition to the Hospital and its Board of Trustees, and show appreciation for what they had done. "When the University of Toronto has to-day honoured me with this degree of Doctor of Laws, my cup of gratitude is overflowing."

Immediately following Convocation, a reception and garden party were to have been held in the Quadrangle of University College, but as an unexpected rainstorm came on, arrangements had to be made to carry out this event in the entrance hall and corridor of University College. After a brief delay, guests were received by the Chancellor, Sir William Mulock, the Hon. and Rev. H. J. Cody, and Dr. F. G. Banting. Refreshments were served with some difficulty, but everybody understood the unforseen disturbance of arrangements and enjoyed the picnic character of this feature of the programme. About 300 attended this function.

In the Great Hall of Hart House, the Board of Governors of the University entertained at dinner the recipients of Honorary Degrees, the delegates from other Universities and Medical Colleges, members of the British Medical Association (Tour C), representatives of the Provincial Government, the City of Toronto, Medical Associations and Licensing Boards, Trustees from Hospitals, the Heads of other Faculties and Colleges, and the Faculty of Medicine, over 200 sitting down.

The Hon. and Rev. H. J. Cody, Chairman of the Board of Governors, presided.

After the toast to the King, Lord Moynihan of Leeds, proposed the toast to the University of Toronto, which was responded to by Dean A. Primrose. The toast to Sister Universities was proposed by Professor W. E. Gallie, head of the Department of Sugery, and responded to by Professor Robert Muir, Professor of Pathology at Glasgow, on behalf of the British Universities, by Professor F. P. Gay, Professor of Bacteriology at

Columbia University College of Physicians and Surgeons, New York, on behalf of the United States Universities; and Professor J. C. Meakins, Professor of Medicine, McGill University, on behalf of the Candian Universities.

Professor Duncan Graham, Professor of Medicine, proposed the toast to Our Guests, which was responded to by Professor Arthur H. Burgess, immediate Past President of the British Medical Association; by Col. Sir William Taylor, President of the Royal Academy of Medicine in Ireland; by Dr. Robert Hutchison, Royal College of Physicians, London; and by Sir Ewen MacLean, Past President of the British Medical Association.

The Story of Insulin.

By J. C. Thomas, M.A., 3T1.

Insulin is an extract of the islet tissue of the pancreas used as a treatment for diabetes. This fact has become so familiar that little attention is now given to the attempts to isolate this hormone, culminating in the success of Banting and Best at Toronto in 1921. Yet the story of the discovery of insulin ought to be of sufficient interest to justify a brief review of the literature even at the risk of repeating what may already be familiar to many.

Langerhans first described the isles of the pancreas in 1869 but did not venture to express any definite opinion as to their physiological significance.

Laguesse, in 1893, and Diamare, in 1895, were the first to state definitely that the islets produce an internal secretion. This view was accepted by E. S. Schafer (1893), who suggested in 1916 that the internal secretion should be named "insuline."

The repeated clinical reports that a pathological condition of the pancreas is present in severe diabetes prompted many investigators to try to produce this condition in animals by removal of this organ. The first successful results were published in 1889 by von Mering and Minkowski, and in 1893 the latter described in detail the technique of the operation together with the diabetic condition which supervenes. He also pointed out that partial removal of the pancreas causes no diabetes unless the greater part of the pancreas is removed. This type of experimental diabetes has been investigated more particularly by F. M. Allen. The first two authors attributed the condition to removal of an internal secretion. The course of the diabetes produced by complete pancreatectomy is more severe than that usually observed in man and it is extremely acute from the start. Partial removal produces a mild diabetes.

The first change occurring after pancreatectomy is the removal of almost all the glycogen store of the liver, and no glycogen can be stored there even when an excess of carbo-hydrate is fed. Following the disappearance of glycogen, glycogenesis sets in and the animal converts its tissues into glucose. The blood sugar is high (hyperglycemia) and sugar is excreted in the urine (glycosuria). The percentage of ketone bodies (oxybutyric acid, aceto-acetic acid, and acetone) increases in the blood and they appear in the urine. Such an animal provides a valuable experimental subject upon which to investigate diabetes.

As early as 1892 Minkowski published the results of experiments in which he had failed to observe any remedial action to follow injection into depancreatized dogs of extracts of the removed glands. Many subsequent workers continued the search for this

hormone. Some tried feeding raw pancreas while others used an extract. Certain workers reported favorable results but were contradicted by others. Until 1898 the results were contradictory but mostly negative.

More hopeful results were obtained about 1898. Lepine found that the injection of lymph from a normal dog caused, when injected intravenously, a certain degree of disappearance of sugar from rabbits, and concluded that a glycolytic ferment must be present in it. About this time Blumenthal came closest to the discovery of insulin. He treated the expressed juice from the pancreas with alcohol to remove some of the proteins. This extract when injected into animals and diabetic patients gave evidence of increasing the utilization of sugar, but it was not followed further because it had such violent toxic effects.

Zuelzer and his collaborators devised a means of extracting a substance from the pancreas which relieved the diabetic symptoms when injected intravenously. However, such severe toxic symptoms developed that further use of these extracts on diabetic patients was abandoned.

Scott set out with the idea that the digestive enzymes may destroy the anti-diabetic hormone of the pancreas. He first tried ligating the pancreatic ducts, but after finding that atrophy of the gland was incomplete, he changed his plan and tried destroying the enzymes with alcohol before making his extract. He succeeded in showing that the extract lowered the urinary sugar, but no convincing results were obtained.

Thus from 1889 to 1913 the attempts to prepare an extract of the pancreas which would be anti-diabetic were without practical success, yet not complete failures. A spark of hope remained, and it was kept alive by the coincident researches of anatomists and other experimenters who persisted in the view that the isles of Langerhans are the organs upon which the anti-diabetic function of the pancreas primarily depends.

Between 1913 and 1916 Murlin and his associates continued the search. They used a saline extract of ox pancreas and found that it caused complete disappearance of sugar from the urine of a depancreatized dog. In subsequent experiments the extracts were made alkaline before injecting them and it was thought that the fall in excretion of sugar might be due to the alkali alone. This proved to be just a coincidence, but diverted their attention for several years tc the effect of alkali.

Thus the search for an anti-diabetic extract of the pancreas had been carried on for about thirty years with hopeful, if not entirely successful results. While these researches were being carried on, physiological methods and knowledge were increasing. Several methods were elaborated whereby the percentage in sugar in a small sample of the blood might be estimated. Studies in metabolism were being carried on and systems of dietetic treatment of diabetes were being developed.

On April 14, 1921, Dr. F. G. Banting began working in the Physiological Laboratory of the University of Toronto on the extraction of an anti-diabetic substance from the islet cells. His associate was Dr. Charles Best. Their first step was to ligate the pancreatic ducts in a number of dogs. After allowing time for the degeneration of the acinar cells the dogs were chloroformed and the pancreas was removed from each. These were found to be about one-third the original size, shrivelled and fibrotic. This material was cut up into small pieces, ground with sand, and extracted with normal saline. The extract was tested on depancreatized dogs, observing the blood sugar and urinary sugar. By intravenous injections the blood sugars were reduced to normal or subnormal levels and the urine became sugar free. The dogs also showed marked improvement in general condition.

The success of this extract support-

ed the view that trypsin destroyed the anti-diabetic principle in the extract. This led to the second type of extract which was made from the pancreas of dogs in which the acinar cells had been exhausted of trypsin by the continued injection of secretin. However, it was not always possible to completely exhaust the acini of the gland and toxic effects frequently developed.

Knowing that there were comparatively more islet cells in the pancreas of the newly-born than in that of the adult, the third type of extract was made from foetal ox pancreas. Decided anti-diabetic effects were obtained from these extracts. It was then found that alcohol, slightly acidified, extracted the active principle and by applying this method of extraction to the whole adult beef pancreas, active extracts comparatively free from toxic properties were obtained.

Depancreatized dogs seldom live more than 10 or 12 days, but with the daily administration of this whole gland extract a depancreatized dog was kept alive and healthy for ten weeks. This dog was then chloroformed and a careful autopsy failed to reveal any islet tissue.

The extract was at this time of sufficient purity to be tested on diabetic patients at the General Hospital. There was marked reduction in blood sugar and the urine was rendered sugar free, but the high protein content made the continuous use undesirable due to formation of sterile abscesses. At this stage, the whole laboratory of the physiology Department under Professor Macleod, was given over to the investigation of the physiological properties of insulin. Dr. J. B. Collip succeeded in purifying the active principle by fractional precipitation with alcohol. Dr. Best then took up the production of insulin on a large scale.

Steps were taken by the University of Toronto to insure the proper manufacture of insulin and to provide for some measure of control over its distribution among physicians. After it was discovered that an active non-irritating preparation of insulin could be prepared on a small scale as outlined above, attempts were made to expand the scale of production. Great difficulties encountered were at last overcome and when a reliable large scale procedure had been definitely elaborated in detail, the question of publication of the method came to be considered. It was pointed out that such publication of the method would probably result in some commercial firm modifying the process sufficiently to obtain a patent which would give it a monopoly in manufacture. The only satisfactory way to prevent this was for the chief originators of the method to apply for such patents in their own names and to assign these, when granted, to some non-commercial organization to administed in such a way as to prevent commercial exploitation of the product. Applications for process and product patents were, therefore, filed in Canada and the United States, and the Board of Governors of the University of Toronto was requested to accept these patents and to assume responsibility for their administration. The Board of Governors accepted this trust and created a body known as the Insulin Committee, with an advisory committee.

One of the first questions to be considered by the committee related to further expansion in the manufacture of insulin. It was decided before issuing licenses to manufacturers, to develop the details of a large scale method of production to insure a product of constant potency. At the same time it was realized that adequate facilities for doing this on a practical manufacturing scale could not be provided for unless by collaboration between the committee and some highly organized firm or firms engaged in the manufacture of such products. Since it was evident that such collaboration could not be carried out satisfactorily with several firms, it was decided to invite the Eli Lilly Company of Indianapolis

to send representatives to Toronto to confer on the question. An agreement was entered into by which this firm was granted an exclusive license in the United States for the manufacture of insulin for an experimental period set provisionally at one year, under the conditions that:

1. The firm utilize all of its available facilities and personnel for the manufacture of the product and pay all expenses entailed in its large scale manufacture in their plant.

2. The firm submit samples of its product to the University of Toronto for approval before distribution to physicians for use on patients.

3. The approved product to be distributed either gratis or at cost price only to such physicians as may be chosen in consultation with the University of Toronto.

4. A certain percentage of the approved product be given gratis to the University of Toronto for use in its experimental laboratories and for clinical purposes in its associated hospitals.

5. At the expiration of the experimental period the firm be licensed by the University of Toronto to manufacture the product under the same favorable terms as may be granted to other firms operating in the same territory.

In consideration of the acceptance of the conditions contained in an agreement signed May 31, 1922, all known details of the method of manufacture of insulin were given to the Eli Lilly Company, and work was immediately started by it on a large scale.

During the latter part of 1922 intensive work on the manufacture of insulin resulted in the gradual increase of the output so that it became possible to offer insulin for clinical trial to a larger number of physicians, whose reports on its therapeutic value have proved to be of great value in guiding the committee and the manufacturers in questions of suitable dosage, possible risks from overdosage, and the elimination of irritating impurities.

By adopting this policy exploitation has been prevented and products of uniform purity and potency were available for clinical purposes after a comparatively short period of time.

In the Connought Laboratories insulin is prepared exclusively from ox pancreas. Fresh glands freed from excess fat and connective tissue are obtained each morning from the city abattoirs. At the abattoirs the glands are collected every hour and placed in a refrigerator at 4°C.

The glands are weighed and then run through a power meat chopper. The minced material is dropped into large earthen crocks and extracted with acid-alcohol. After standing over night the acid-alcohol mixture is poured into a large rotary centrifuge which separates the alcoholic extract from the solid materials. The extract is made alkaline with ammonium hydroxide and filtered. The filtrate is then acidified with sulphuric acid. The alcohol extract is then concentrated to about one-tenth its original volume in a vacuum still at low temp.

After distillation the concentrate is treated to remove lipoid and other materials. Ammonium sulphate is then added to half-saturation, and on stirring protein material separates out and rises to the top of the liquid. After standing over night the protein precipitate is skimmed off and as much liquid as possible is pressed out. The weight of the precipitate from 300 lbs. of gland is approximately 200 gms.

This precipitate contains active insulin which is now purified by a long process, using alcohol and isoelectric precipitations until the final precipitate is obtained. This is dissolved in water and the pH adjusted. Salt and tricresol are added and the solution is sterilized by passing it through a Seitz filter. The potency is estimated by the method of assay described later. After determining the strength of insulin the solution is diluted with

acid water so that each c.c. contains 10, 20, or 40 units. The solution is again passed through a Seitz filter. The insulin is then poured into sterile glass vials with aseptic precautions and the sterility of the final product thoroughly tested.

The potency of insulin extract is measured by a method of bio-assay, using the rabbit as a test object. In the Medical Building there is a testing laboratory for insulin produced in Canada and the United States with the power to exercise control in Great Britain. International uniformity in dosage has been assured by conference among the testing authorities through the Permanent Standards Committee of the Health Section of the League of Nations. A dry preparation of insulin hydrochloride has been prepared by the Medical Research Council for the purpose of establishing a standard. Its assay has been found to be such that 1 mg. equals 8 units. The international standard is kept under the auspices of the Health Committee of the League of Nations and from time to time testing laboratories will have the opportunity of having standards compared with it.

At Toronto the following plan is followed when standardizing insulin: Rabbits of either sex and any breed, free from any infection, weighing 1.8 to 2.2 Kg. are used. They are used once a week as suitable. The diet consists of hay and oats with carrots once a week for the first post-assay meal. All new rabbits are kept on this diet for two weeks prior to first time in use. Twenty-four hours before being used all food but water is withheld.

With a new lot of insulin of unknown strength a rough estimate is first obtained by injecting 18 rabbits with widely varying doses and noting lowest dose to produce convulsions in the majority of animals. This so-called convulsive dose is considered very roughly equal to 3 units. Starting with this as an approximation the determinative assay is run, using 18 rabbits each day. Nine are injected with a standard corresponding with the International standard kept in form of dry powder and nine are injected with the unknown. Each is weighed and normal blood is taken before injection. Three doses of insulin diluted with water so that presumably 1 c.c. contains 2.5 units, are injected subcutaneously into three groups of three animals each, 2.5, 2.0, and 1.5 units per 2 Kg. body weight being given to each animal of first, second, and third groups respectively.

Similarly three doses of standard insulin diluted with acid water, so that 1 c.c. contains 2.5 units, are injected as above.

At one and a half, three and five hours after injection a blood sample is taken from each and sugar content is determined. From a formula which takes account of fall in blood sugar, body weight, and dose injected the unit value is calculated.

If unknown and standard results differ greatly it is necessary to re-essay with a new dilution on basis obtained for unknown so that on final analysis the results of unknown and standard should be approximately equal.

At present a minimum of four days of final assay is carried out with an alternation in rabbits by which those receiving standard on first two days get the unknown on the second two days and vice versa.

With the improvement in the quality of the insulin available, the increased knowledge of its physiological properties and increased quantities being prepared, the clinical investigation was undertaken extensively. Clinics were established at Christie St. Hospital, the Toronto General Hospital, and Hospital for Sick Children. It is beyond the scope of this paped to even attempt to summarize the early clinical findings in the treatment of diabetic patients with insulin. It is sufficient to say here that it was found that insulin increases the carbohydrate tolerance of the diabetic so that the

amount of carbohydrate in the diet can be increased and the patient gains rapidly in strength and weight.

Summary.

A brief sketch of the attempts to isolate an anti-diabetic hormone from the islet cells of the pancreas is given.

The successful researches of Banting and Best are outlined with a description of the present method of preparation of insulin on a large scale.

The patenting of the process of manufacturing insulin and the administration of these patents are described.

A synopsis of the control of potency and standardization of the extract is given.

Diverticulosis and Diverticulitis.

By H. N. Taube, 3T1.

This paper is a review of the literature from Jan., 1916, to March, 1930, on Diverticulosis and Diverticulitis. The word diverticulum, as applied to the digestive tract, means a non-neoplastic outpouching of the intestine with a lumen that does or did connect with the bowel.

Diverticulosis is a condition in which there are numerous small pouches or protrusions in the walls of the colon which are demonstrable by examination with a barium enema under the X-rays, but which is not accompanied by any symptoms referable to the diverticula. Diverticulitis is the condition in which inammatory changes have taken place in the diverticula, and definite symptoms attributable to these changes are complained of by the patient.

History.

Diverticula have been noted by various observers for more than a century, but for the most part as isolated cases. The condition was looked upon as a rare pathological curiosity of no real clinical importance. The more frequent adoption of X-ray examination has shown that the disease is more common than is generally realized.

Cruveilhier was the first to recognize the disease, in 1849. The condition was recognized and described also by Virchow in 1853. Windshield in 1889 added further description of similar cases, but it was not till Graser in 1899, demonstrated the association of acquired diverticula with these pathological changes that a clear understanding of the condition was attained. Since then many writers, notably Beer, Telling, Moynihan and others, have added materially to the knowledge of this pathological condition. In 1907 Mayo and Wilson reported the first series of five American cases for which operation had been performed. According to James and Case, the first case operated upon after previous radiological demonstration was published by Abbe, the radiological examination being carried out by Le Wald, who in 1915 made the first X-Ray diagnosis of diverticultis of the colon. Carmen was the first roentgenologist to report a series of cases examined by the roentgen ray, and the first to formulate a scheme for the recognition and differential diagnosis of diverticulitis.

Etiology.

Diverticula may occur in any part of the alimentary tract. They are rare in the stomach and small intestine; but are common in the large intestine, more especially in the sigmoid colon. It is in this region that they most frequently cause symptoms. They are very uncommon in the rectum, owing to the thickness of the muscular coat.

Various factors have been held to play a part in predisposing individuals to this condition. Among these are:

1. *Age.*—Diverticulitis is essentially a disease of later middle age, between the ages of 45 and 65.

2. *Sex.*—The condition occurs chiefly in men, in the ratio of 3 to 1.

3. *Constipation and Aperients.*—Constipation has been given as a cause. Constipation is such a common symptom, particularly in late middle life, that not much importance can be attached to it as a factor in the production of diverticulitis.

4. *Obesity.*—Obesity by some is regarded as a cause of weakness of the gut, and therefore an important factor in the production of diverticula. Price believes that "the presence of fat diminishes the resistance of the intestinal wall to pressure from within, so that the diverticula are especially likely to occur in the obese."

This viewpoint is supported by Dr. Davies Colley, who says that "diverticula never occur when the intestinal wall is covered by peritoneum alone." W. J. Mayo points out that not much significance can be attached to obesity as an etiologic factor, inasmuch as the percentage of patients who were underweight was about the same as that who were overweight. In a series quoted by Spriggs, there was no evidence that diverticulous patients are fatter than others of the same age or that the fat-laden bowel offers less resistance to the early stages of the disease; yet the average weight in a large series from the Mayo Clinic was about 170 lbs. It is highly probable that more diverticula occur in fat-laden bowel than in that possessing poor fatty covering, the fat weakening the musculature by causing gaps between the fibres.

5. *Heredity.*—In some individuals there exists an hereditary constitutional weakness in the smooth muscular portion of the wall of the hollow viscera.

Exceptions occur to all of the above statements. Youth, lack of obesity, lack of constipation, do not preclude the existence of the condition.

Several theories have been advanced to explain the formation of acquired diverticula.

A. *The Vascular Theory.* — Hansemann and Klebs were the first to call attention to the fact that the protrusions were closely related to the blood vessels entering and leaving the intestine along the mesenteric border. However, it has been pointed out by other observers that not all protrusions bear this relationship to vessels, and this explanation cannot, therefore, be applied to all cases.

B. *Degeneration Theory.* —Lochart-Mummary is of the opinion that the initial factor which starts the formation of true pulsion hernia or diverticula is probably some degeneration of the bowel wall from age and unnatural conditions of the bowel function. That the condition is practically confined to the second half of life and that diverticula of the colon are frequently seen in fat people, favour this view. Moreover, Hansemann showed that diverticula could be produced experimentally under similar conditions in intestines of senile subjects, but not in those of young subjects.

C. *Increased Pressure .Theory.*—A popular view is that diverticula are the result of increased pressure within the bowel; this may be due to the accumulation of faeces or the increased tension of gas. Rowden points out that due to the weak muscular development, the colon, in man, exerts and withstands small pressure. For efficiency, the colonic contents should be maintained in a soft condition. If more than 80% of water is observed, the colon alone cannot expel its contents; it requires the assistance of the voluntary abdominal muscles. For only a short time can the weak musculature of the colon withstand this additional force. Consequently the mucous membrane is gradually forced through the weakest points. In support of this idea he demonstrates that they occur most frequently in the sigmoid colon, where

the greatest force is exerted by the contraction pressure of the abdominal muscles, and where the fecal stagnation tends to be greatest. The sigmoid colon is the chief "delay point" in the intestine; the stools are becoming firmer and less moist; and the formation of gas is often considerable.

Keefe states that the pressure of formed fecal matter in the sigmoid may be an important factor in the production of diverticula, but fails to explain the presence of diverticula in the ascending and transverse colon, where the contents are fluid.

D. *The Infectious Theory.*—The discovery of the pre-diverticular state by Marxer in 1921 altered the existing conception of diverticulosis. As a result of microscopic and radiological evidence they believe that, antecedent to the formation of pouches, a local irritation or inflammation attacks the bowel wall and that this weakens or thins definite areas and so predisposes to herniation.

That diverticulosis may be due to or associated with a chronic infective process is indicated by its frequent association with various infective states elsewhere, particularly with arthritic changes in the spine and with apical abscesses. Moreover, it has been suggested that septic absorption from purulent material in infected diverticula give rise to, or favour, sepsis in other parts of the body.

The part played by pressure and constipation, the blood vessels, and the congenital weakness of the wall of the colon, in the production of these diverticula has been widely discussed, but most observers agree that a change takes place primarily in the resistance powers of the wall. This change is probably slow and does not result in true diverticula until middle life.

Pathology.

Diverticula of the alimentary tract fall into two types: (1) congenital, (2) acquired. The former has been known and described for many years. Diverticula of the colon which set up diverticulitis are no longer considered congenital in origin: (1) they practically only occur after middle age; (2) long continued X-ray study has shown that the condition often progresses into normal areas of the colon.

Diverticula may be found in any part of the gastro-intestinal tract; diverticulitis is restricted to the sigmoid colon, particularly the distal portion down to the junction with the rectum, where it stops abruptly due probably to the absence of appendices epiploicae and a stronger musculature. Occasionally it may continue into the rectum.

Spruggs and Marxer divide the progress of the disease into three stages:

(1) The pre-diverticular stage.
(2) The stage of formed diverticula.
(3) The stage of inflamed diverticula, or diverticulitis.

Each of these stages grades into the next; and, all of these stages may be present in different parts of the bowel, or even in the same segment.

Marxer has shown that the onset of the disease can be recognized often before the little pouches have formed. This is the pre-diverticular state which can be diagnosed only by X-ray.

The diverticulum starts probably as a hernial outpushing of the mucosa, either through or accompanied by the muscular coat (one or both layers) and covered externally by the serosa. These pouches are variable in size from that of microscopic visibility to that of plum stones, and variable in number, but as a rule they occur in large numbers. Very early the pouch acquires flask shape, the neck being narrower than the distal body. The orifices are usually quite small, and often partially or completely concealed by the circular folds of the lumen. The quickest growth and the largest sacs are seen in patients with loose stools; probably such pockets fill and empty oftener. Frequently the pouches may be confined to the appendices epiploicae, which are frequently filled with fat, and so are areas of lessened resist-

ance. Pouches in this situation contain mostly faeces, of varying degrees of hardness and inspissation, and often causing trouble even when microscopic.

Secondary Pathological Processes.

Secondary Pathological processes can be divided into two groups: (1) Mechanical (mainly); (2) Inflammatory (mainly).

Both processes may go on in the same case.

1. Mechanical:
   - (a) Formation of fecal concretions in the diverticula.
   - (b) Torsion of the diverticulum.
   - (c) Lodgement of foreign bodies within the diverticular sacs.

2. Inflammatory:
   - (a) Diverticulitis: 1, gangrenous; 2, acute; 3, subacute; 4, chronic; 5, latent.
   - (b) Passage of organisms without perforation.
   - (c) Periderviticulitis—chronic proliferative inflammation with tendency to stenosis of the bowel.
   - (d) Perforation of the diverticula, giving rise to
     - (1) general peritonitis,
     - (2) local abscess,
     - (3) fistula, especially into the bladder (rare),
     - (4) suppuration in a hernial sac.
   - (e) The formation of adhesions, especially to:
     - (1) small intestine,
     - (2) bladder,
     - (3) female genitalia.
   - (f) Chronic peritonitis, local.
   - (g) Chronic mesenteritis of the sigmoid loop.
   - h) Metastatic suppuration (rare).
   - (i) The development of carcinoma.

A diverticulum need not progress. If the diverticulum enlarges the muscular coat may disappear. Owing to the shape of the diverticulum, a sac with a narrow neck, the fecal contents may be retained, particularly in the drier portion of the bowel. Here they become hard and often stony. This condition predisposes to certain mechanical results, especially perforation.

The most frequent secondary change and probably the first change in the diverticulum is an inflammation of variable type and intensity. This is due to mechanical irritation by the fecal mass and to infection. The narrow neck, and inflammatory or toxic oedema of the lipped orifice cause very poor drainage of the sacs, leading to acute or gangrenous, or latent or chronic inflammation. Sometimes a slight inflammation in a thinned pouch may permit the passage of micro-organisms to the peritoneum causing peritonitis. Occasionally a diverticulum may perforate suddenly, giving rise to general peritonitis, the so-called pistol-shot type of perforation. The inflammatory changes in a diverticulum are practically identical with the changes which may occur in the appendix. For this reason diverticulitis has been called the left-sided appendicitis of old people.

When the pouch becomes inflamed, and faeces accumulate in it the mucosa becomes thin and ulcerated, the muscle atrophies, the ulcer may perforate and cause a local abscess (about ten per cent. go on to abscess). This abscess may enlarge until it ruptures into the intestine, or may seal itself to the abdominal wall and perforate into the general peritoneal cavity, or it may burst into the bladder causing a colovesical fistula, so that faeces and gas pass through the urethra.

Together with an inflammation of the sac wall, there may be a low grade, chronic, hyperplastic inflammation around the diverticulum. This process, called peri-diverticulitis, is caused by a leaking into the tissues of bacterial toxins through damaged sac walls. It may become very marked, and may surround a section of the gut with a constricting band of fibrous tissue, leading to tumor formation by hyper-

plasia and stenosis of the gut by contraction.

Tumor is noted in about 30 per cent. of the cases. These tumors are always adherent to other structures, and are generally situate at or near the middle of the sigmoid flexure.

An attack of diverticulitis with threatened obstruction may occur as a result of two conditions: local inflammatory swelling of only the mucosal folds, or rigid fibrous contraction of the whole bowel wall, usually accompanied by swelling of the small folds of the mucosa. The second condition is associated with chronic dilatation of the gut above the construction.

Judd and Pollock believe that diverticulitis does not predispose to carcinoma. Dr. George Wilson is of the same opinion. The presence of diverticula does not exclude the existence of carcinoma.

Radiological Picture.

Since the introduction of the barium enema in the examination of the distal part of the colon, diverticulitis is being more frequently diagnosed as a cause of lower abdominal symptoms.

A complete and definite diagnosis can be made only by means of exploratory laparotomy and microscopical examinations of an excised portion of the effected bowel or by means of X-ray examination. Roentgen-ray study is an important means of detecting diverticulosis and diverticulitis. There are two methods of X-ray examination, the opaque meal and the opaque enema; the former will demonstrate the presence of diverticulosis, but not, as a rule, that of diverticulitis; the latter will demonstrate diverticulitis. It is more satisfactory to employ both methods and to use both screen and roentgenographic study.

The earliest change in the appearance of the bowel in diverticulitis is an alteration in the haustration. Instead of being placed opposite one another, the haustral indentations alternate on each aspect of the bowel. Secondary smaller indentations also make their appearance. This is the stage of irritation. The bowel presents a more rigid outline.

In the second stage of formed diverticula (diverticulosis), the diverticula are seen as rounded shot-like portions of opaque salt, particularly on the 2nd or 3rd day after the opaque meal has left the lumen. The pouches may retain bismuth up to the 16th day or longer. The omission of this last film in routine examination (on 2nd or 3rd day after opaque meal) has led to underestimation of the frequency of the disease.

The radiological features of diverticulitis (the 3rd stage) are definite. With a barium meal or enema, rounded, oval, or crescentic shadows of the barium will usually, though not always, be recognized in the pouches. They are not, however, the characteristics features; these are:

1—the rounded or serrated translucent intrusions into the barium-filled lumen due to swollen mucosal folds, or

2—spike or palisade-like projections of barium shadows from the lumen of the bowel, the wall of which is fixed and thickened from inflammatory exudation. These shadows represent deformed and contracted haustra. In this form several films show no variation in the outline of the shadows. With each exacerbation of symptoms there is often a new attack of diverticulosis and this can be seen close to the old areas of disease.

If one definitely suspects diverticulitis but finds no sign of the diverticula with the opaque meal, it may be helpful to give the maximum physiologic dose of belladonna or atropine during 24 to 48 hours. Then the usual preparation of the colon by cleansing enemas will considerably increase the chance of demonstrating the diverticula by the opaque enema. The use of the antispasmodics will also aid in differentiating between an organic stric-

ture and a spastic state, a differentiation very important to make but not always easily accomplished in diverticulitis. It must be borne in mind that a negative X-ray finding does not exclude diverticulitis, for the barium in the pelvic loop or rectum may mask the defect. Only by repeated injections will the barium enter the diverticula, if they be small mouthed or if they be loaded already with hard fecal material.

Symptoms and Signs.

The pre-diverticular state has no peculiar symptoms. Diverticulosis, the simple presence of diverticula of the colon, gives rise to no symptoms. Diverticulitis and its extensions give rise to a variety of symptoms. However an advanced state of diverticulitis may be present with little complaint.

The temperature is often slightly raised to between 99 and 100. In acute exacerbations, it may be very high and accompanied by severe constitutional symptoms. Even in the more chronic cases, a polymorphonuclear leukocytosis is generally present. When the bladder is attacked, there may be frequent micturition, sometimes painful. This symptom may due to adhesions of the inflamed gut to the bladder, but may be independent of this condition. At a later stage, cystitis may occur, and in rare cases go on to a vesico-colic fistula, diverticulitis being a more common cause of this condition than cancer of the colon. The symptoms of all vesico-colic fistulae are:

1—Passage of gas and feces through the urethra, the former may be so great as to cause "roaring" in the bladder.

2—Passage of urine through the rectum. These patients usually complain of intense pain on urination, due probably to cystitis and the passage of hard fecal particles irritating the neck of the bladder and urethra.

Diverticulitis has been classified clinically into three types: (1) the enterospasm type; (2) the hyperplastic type; (3) the pseudo-appendicitis type.

The enterospasm type includes that group of cases in which the pouches are scattered and the symptoms apparently those of enterospasm, kept up by continuous intestinal irritation. The early symptoms of this group are common to the early stages of many abdominal diseases, vague abdominal distress, slight intestinal upsets, discomfort in the abdomen, particularly on the left side. A well developed diverticulitis causes attacks of pain and tenderness over the entire colon, usually more marked in the left lower quadrant, frequently combined with distress in the right lower quadrant. Bladder irritatibility is frequent and associated with tenderness over the middle of the lower abdomen. This abdominal tenderness is encountered very commonly and is accompanied often by muscular rigidity. Colics are not rare and when present recur frequently. Attacks of irregular fever may recur periodically. Leukocytosis may occur with or without fever. Constipation is usual though it occasionally alternates with diarrhoea. Examination of the stools in this group seldom reveals the presence of blood. In diverticulitis with enterospasm predominating, there is no urgent need for surgery.

In the "pseudo-appendicular type," the pouches even without peridiverticular inammation became acutely inflamed like acute appendicitis. This group includes inflammation of an epiploic tag. In this type, the patient, usually with a long history of diverticulitis of the spastic type, suddenly develops acute symptoms demanding urgent attention. These symptoms should be distinguished from the true left-sided appendicitis which occurs only with non-rotation of the colon or with true transposition of the viscera. Otherwise the complaints and signs are quite similar; hyperleucocytosis, fever, pain, tenderness usually over the left side, muscular rigidity, constipation occasionally alternating with diarrhoea, localized peritonitis—all suggest-

ing the need of surgical intervention, at least for drainage of the infected area.

The hyperplastic type refers to those cases in which an obstructive tumour is produced. In the region of the pelvic colon, the pouches are fairly close together and so are subject collectively to the peridiverticular inflammatory reaction, and the subsequent production of connective tissue. In this type the symptoms are those of a long-standing constipation with perhaps a history of several acute attacks stimulating the so-called left-sided appendicitis. The hyperplastic type is characterized by progressive obstinate constipation, the development of colicky pains, notably across the transverse colon and in the right side of the abdomen, small, frequent stools or impulse to move the bowels without good results, and usually a palpable tumor. This tumor is generally described as sausage-shaped, tender and not as a rule mobile. Its variability in size within a few days, is one of the most reliable signs of perisigmoiditis due to diverticulitis. This tumor may be felt either abdominally, rectally, or on a combined examination.

Abscess is of very frequent occurrence (28 per cent.) and frequently leads to tumor formation. It is responsible for the pyrexia and leucocytosis and also for the spontaneous disappearance of both tumor and symptoms.

While diverticulitis is more commonly encountered on the left side, the condition is by no means confined to the descending colon and sigmoid.

Harbin points out that in the acute abdominal conditions there is an incidence of 1 per cent. of diverticulitis of the descending colon. Acute conditions in the left abdomen should suggest the probability of a diverticulitis of the colon. Robert states that every "pot-bellied individual over 60 should be suspected of diverticula in the colon, particularly if there is a history of long standing constipation and lower abdominal discomfort."

Diagnosis.

The diagnosis in a typical case is fairly easy. The patient is generally a well nourished male between the age of 40 and 65. There is a long history of attacks of left-sided abdominal pains with intervals of well being. There may be attacks of diarrhoea alternating with constipation. Usually blood or mucus is absent from the stools. Any left-sided abdominal tumor, especially if it shows acute swelling and intermittent pain, should be investigated for diverticulitis. There may be bladder irritability, leucocytosis and pyrexia. In all chronic cases except those which have gone on to abscess with severe constitutional symptoms, a competent X-ray examination, if obtainable, is essential, and establishes the diagnosis. The common errors are diagnosis of diverticulosis because some diverticula are seen and failure to diagnose diverticulitis because the piece of bowel affected is not brought into profile. The sigmoidoscope is of value only in differential diagnosis. All cases of persistent abdominal discomfort should be X-rayed. Advanced diverticulitis can often be recognized clinically, but the diagnosis can be made certain only by a barium enema.

Differential Diagnosis.

(1) In the differential diagnosis, malignant disease is most important. An early growth of the sigmoid in a patient who has lost very little weight may give rise to symptoms similar to those of diverticulitis.

The two are distinguished radiologically:

(i) In diverticulitis there are pouches near the deformity in the outline of the bowel; in carcinoma pouches are absent usually.

(ii) Diverticulitis produces a characteristic deformity. A growth produces a variable deformity.

(iii) Diverticulitis usually affects a considerable length of the bowel;

carcinoma usually affects the bowel for only a short distance. They may occur together.

Clinically the differential diagnosis between carcinoma and diverticulitis is:

In carcinoma there is progressive wasting, and very frequent occurrence of blood in the stools. In diverticulitis, on the other hand, there is a history of repeated attacks with more or less fever, a long history of "capriciousness of the bowels," no cachexia, intermittency of attacks. Furthermore cancer rarely causes pain or tenderness. The inconstancy of the tumour is characteristic of diverticulitis, according to Mayo clinic statistics for the years 1924-28.

(2) Sigmoiditis—can be distinguished only by operation or autopsy findings.

(3) Left-sided Appendicitis—usually occurs with complete visceral transposition. Exploration may be necessary.

(4) Actinomycosis—usually attacks the caecum, and occurs at any age. There may be ray-fungi in the stools.

(5) Syphilis—is very rare in the sigmoid flexure and is further distingushed by the presence of other signs, the Wasserman reaction, and therapeutic tests.

(6) Hyperplastic tuberculosis of the large bowel is confined to the caecum.

(7) Pelvic lesions. Tumors and inflammation of the adnexa in the female may be distinguished by gynecological examination and history.

Prognosis.

A favourable prognosis of diverticulitis depends on early recognition and treatment. In all cases the disease can be arrested indefinitely by suitable treatment. In localized advanced disease with a too narrow lumen of the bowel, resection may give complete relief. In others, colostomy should be done. If abscesses have formed and there are severe constitutional symptoms, the outlook is grave.

Treatment.

Medical Treatment. The treatment of an early case of diverticulitis is the same as that of diverticulosis, "keep the body, generally, and the bowel, particularly, as healthy and clean as possible." The diet should be simple and regular with a good deal of fruit and vegetables and little meat. Meat is given 2 or 3 times a week to begin with, but later added daily, if desired, provided the bowel movements are regular. If inflammation of the mucosa makes fruits, greens or wholemeal bread undesirable, a bland diet of cereals, milk and fish or meat is needed. Such a diet relieves the bowel of work. This is unfortunate because contractions promote the health of the gut and prevent stagnation of faeces in the lumen and pockets. A small amount of fruit puree, or greens will help to keep the bowels regular when aided by paraffin to grease the pouches and ensure that the motions are soft. Altering the flora of the gut by vegetable foods and B. Acidophilus in milk seems to be good. Irritable purges are harmful. Attention to habit is especially important. The colon is washed out with normal saline every other day for a time, but at low pressure. In no case should a diverticulous area be massaged. The patient is told to try to have an action at the same time every day, without straining. If unsuccessful, he should use a glycerine suppository, wait 10 minutes, and try again. If this fails, an enema may be used. The patient's life must be regulated as to work, exercise and adequate rest, with the object of improving the tone of the body and the bowel.

During an attack, the patient must be kept in bed on a light diet, with plenty of fluids, and the contents of the large intestine must be liquefied as early as possible by large doses of a saline aperient; the bowel should be washed out by simple enemata, slowly

and carefully. Enemas of 3 to 6 ozs. of warm olive oil or liquid paraffin to be retained all night if possible, are sometimes useful.

After the attack has subsided further trouble may be prevented by proper regime. This has two main objects —the production of a bulky food residue in the colon, and at the same time the reduction of this residue to a liquid form of about the same consistency as that usually present in the small intestine. For this purpose one ounce of liquid paraffin should be taken three times a day and may be expected to produce 2 or 3 loose actions of the bowel daily. The patient must not be allowed to become sufficiently constipated to form a hard stool since this may be followed by another attack of inflammation, with complication. At to diet, the foods that produce a bulky residue and prevent spasm of the colon are to be encouraged, such as brown bread, oatmeal, porridge and vegetables.

In subacute diverticulitis, the symptoms may be gone in a week. The tenderness disappears, the tumor steadily becomes less, and after 3 weeks X-ray shows the lumen is restored almost to normal and the rigid area of bowel is lessened. A more severe inflammation may yield to longer treatment.

All cases should be seen regularly. Spriggs advises an X-ray examination once a year for patients with diverticulosis and once every six months for patients with diverticulitis. Pouches are often harmless and patients with even well-advanced diverticulitis will carry on, year after year, with subsidence of pain and without recurrence of any serious symptom. Careful treatment and careful attention to progress make possible an indefinite period of well-being.

Surgical Treatment. The indications for surgical intervention are:

1. Poor response to medical treatment.
2. Persistent evening rise of temperature with leucocytosis, i.e., persistent infection.
3. Evidence of obstruction.
4. Evidence of threatened perforation into the bladder or into the peritoneal cavity.

Operations, particularly radical ones for diverticulitis, are both difficult and dangerous; the surgeon interferes with diseased bowel which lies often in infected tissue and there is the danger of stirring up the infection that existed around the colon before the operation. It is clear, therefore, that great care and judgment are necessary. Only when serious secondary inflammatory changes have occurred is the surgeon asked to interfere.

Surgical treatment may be divided into conservative and radical.

Conservative treatment. Colostomy well away from the trouble is the safest procedure and should not be dangerous if the diseased bowel is not too thoroughly explored. This is the only justifiable procedure when serious complications, such as local abscess, obstruction, perforation into the bladder, or general peritonitis, have already occurred. In cases of obstruction when colostomy has been done the rest given to the collapsed area, aided by douching, may lead to a great degree of recovery. The swelling subsides and the lumen is restored. Moynihan states that he has found it possible to close the colostomy again in selected cases, to the great relief of the patients. Note.—In cases of abscesses, drain.

Radical Treatment. Radical surgical treatment is sometimes indicated. It is true that the disease tends to spread, but in practice the hypertrophic inflammatory processes are generally confined to one area of the bowel, and if that area can be successfully resected, the patient is cured of diverticulitis Quite often radical treatment is impossible owing to the extent of colon involved and to the unhealthy condition of the colon above and below the lesion. Enfield is of the opinion that wholesale resection of the bowel, ex-

cept in the presence of urgent symptoms, is not advisable.

Resection with end to end anastomosis and temporary caecostomy is the ideal treatment. As an alternative wrapping the diseased tissue in omentum after freeing adhesions will give good results. Operative mortality, particularly with radical treatment, is quite high.

Treatment for vesico-intestinal fistula is essentially surgical. The operation may be palliative or radical. The former consists of colostomy, colotomy, or suprapubic cystotomy. The radical operation consists of intra-abdominal separation of bladder and sigmoid and suture of the openings. The prognosis is always grave.

The following articles were selected by the author from the great number he reviewed, as the more comprehensive ones.

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Disorders of the Thyroid.

By Dr. George S. Young.

Fact and Theory.

The thyroid gland delivers a secretion which is necessary in the regulation of metabolism. The most important ingredient we know in this secretion is iodine, which is taken into the body in water and particularly in food. In certain areas the iodine content of food and drink is low, and here goitre is prevalent. The demand for thyroid secretion (and therefore iodine) varies from time to time and apparently increases, especially at the beginning of puberty. If at this point there is not sufficient available iodine to supply the increasing demand the thyroid becomes hyperactive. This is followed by a resting stage and the deposition of colloid in the aveoli. This process of alternate activity and rest repeats again and again until there is noticeable enlargement of the whole gland due largely to excess of colloid. In this diffuse colloid goitre there may develop areas of somewhat different tissue, the so-called adenomata, which are often palpable as nodules in the softer thyroid structure. Hence the term nodular goitre.

Both diffuse and nodular goitres may remain harmless for a lifetime. They may become locally or generally so large that they exert undue pressure on the surrounding structures of the neck, or even on structures within the thorax. They may be associated with thyroid deficiency, partial or complete. The nodular type may sooner or later become hyperactive and result in the so-called "toxic adenoma." The thyrotoxicosis in such a case is said to be due to the overproduction of a normal thyroid secretion.

But there is another type of enlarge-

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ment associated with hyperthyroidism. The thyroid which hitherto has been of normal size rather suddenly becomes intensely hyperactive. A demand from an unknown source is made for its peak load of secretion. As there is plenty of reserve (as shown by the fact that after operation a small remnant of gland may suffice for the body's need) there may be marked hyperthyroidism without thyroid enlargement. Generally the demand knows no bounds and the gland enlarges diffusely through increase in size and number of its secreting cells. This type differs from the hyperthyroidism of toxic adenoma in at least two respects—exophthalmos and marked response to Lugol's solution. Plummer's explanation is that in exophthalmic goitre there is not only an over-supply of normal thyroid secretion, but also of an abnormal secretion deficient in iodine.

Examination.

The true conformation of the thyroid may be missed because of: (1) Failure to note that the thyroid cartilage or the trachea is not in the midline. (2) Lack of gentleness in palpation. (3) Failure to palpate the whole gland. (4) A low-set thyroid in a short neck.

Unrecognized Hypothyroidism.

The mild case is often overlooked for two reasons: It is not kept in mind as a possibility; the minor symptoms and signs are not looked for. Sterility in women is not infrequently caused by hypothyroidism.

Diffuse Colloid and Nodular Goitre Without Hyperthyroidism.

The simple goitre problem is very important on account of this possible sequence: Diffuse begets nodular goitre, and nodular goitre before it is finished begets toxic adenoma, the end of which is myocardial failure. Prophylactic treatment by small doses of iodine at puberty will sweep simple goitre with its consequences out of existence. The responsibility at present is on the shoulders of the physician and should remain there. Wholesale treatment by the state involves some risks, at least in the light of present opinion. It is thought that even minute doses of iodine may convert the simple adenoma into toxic adenoma. Hence the treatment of simple goitre without nodules should be small doses of iodine up to the age of twenty, and after that, small doses of thyroid, whether nodules can be felt or not. The simple nodular goitre as a rule should not have surgical treatment unless there are pressure signs.

Pseudohyperthyroidism.

There is often considerable difficulty in distinguishing between hyperthyroidism and tachycardia with certain nervous symptoms. In the latter cases, which are variously labelled "irritable heart," autonomic imbalance, etc., the resemblance to hyperthyroidism may be very close. The heart rate is rapid; on the neck may be the patchy shifting erythema so common in hyperthyroidism. The thyroid may happen to be somewhat enlarged. The patient is apprehensive of goitre and the basal metabolic rate if not done repeatedly may be slightly elevated. The following points are invaluable in differentiating the two conditions. The hyperthyroid practically never has cold hands; they are warm and moist. The nervous case has cold, clammy hands. The pulse rate if taken by some one at the patient's home when she is asleep or in the morning before getting up, may be found to be almost normal. In the doctor's office the patient's pulse may show great fluctuation—and especially in a downward direction if her attention is distracted by an interesting story; while in hyperthyroidism the pulse rate is more uniform and is rapid even during sleep. In civilian life these nervous cases are more common in the second decade; the hyperthyroid cases are more often seen after the age of, say, twenty-five.

The Overdriven Thyroid.

Occasionally one sees a young woman who presents a picture of mild hyperthyroidism which is apparently dependent on her living at too high a level, emotionally or otherwise. The stress of business life for a young ambitious girl may make too great a demand on the endocrine system and fatigue may be masked by overactivity of the glands of internal secretion. Here is a girl who takes a position in an office. She is bright and quick in mastering the routine of her work. Her employer gradually unloads his own work on her shoulders. The girl speeds up and finally does the work of two ordinary girls. After a while she finds that she is not sleeping well and cannot sit still. The doctor finds some fine tremor and a rapid pulse, perhaps some eye signs and a full thyroid. Three months' rest in the country will probably restore her to health and a frank discussion of her case with her will probably prevent a repetition of the trouble when she goes back to work.

It would be interesting to know how far these cases would go if left alone. Would the final result be a typical exophthalmic goitre? It is not easy to say, but it is a fact that not infrequently it will be found on careful inquiry that surrounding the onset of a typical exophthalmic goitre there is a setting of extreme mental, emotional or physical strain.

Toxic Adenoma.

Note this common history: Simple goitre in early life. It might have been prevented. Goitre apparently disappeared but a nodule was cunningly hidden behind the sterno-mastoid attachment. In the fourth decade, nervous symptoms and "palpitation" attributedto the menopause. Gradual improvement with occasional return of symptoms. At sixty, myocardial failure. The proper diagnosis is now made, but many years too late. In such a case absolute rest in bed for weeks or months and digitalis in adequate doses may bring the patient to a point beyond which there can be no further progress. Then the patient must decide between a life of invalidism and the risk of operation. If the patient pulls through the operation there is a fair prospect of a moderately active life. Most patients will take the risk. It cannot be repeated too often that the only cure for toxic adenoma is surgery, but it should be invoked long before auricular fibrillation occurs.

Exophthalmic Goitre.

The older physicians have seen many cases recover without operation. I believe that where economic and environmental factors are favourable, where the patient has not reached the age of forty and where the disease has not existed long, medical treatment for three months is advisable. The patient should be most of the time in bed on a liberal high carbohydrate diet. She should be protected from everything that might affect her emotionally. She should have carefully planned mental occupation. It is in such details that general practice becomes a fine art. Sedatives may be necessary but should be given with discrimination. If at the end of three months there has been decided improvement then the patient has been well prepared for Lugol's solution and an operation. Some caution should be used in discontinuing Lugol's solution at any time lest a thyroid storm should be precipitated. It must be admitted that economic and environmental conditions do not often permit prolonged medical treatment of the ideal sort, so that, at the present time, surgery largely has the field.

Conclusion.

Two types of hyperthyroidism have been sharply differentiated, but as a matter of fact between these pure types there are many cases which partake in varying degree of both. Clinical diagnosis is often corrected by

pathological findings. Even the origin and nature of the so-called adenoma is not definitely known. In spite of all this it is helpful to have some clarifying hypotheses such as those presented, viz., that hyperthyroidism may show itself in two distinct entities, which may exist apart or together; and that in exophthalmic goitre there is a two-product secretion, one part of which is normal, the other deficient in iodine.

Control of Erythrocyte Formation.

By R. B. Kerr, B.A., 3T3.

Normal Formation of Erythrocytes.

In the adult mammal, red cell formation occurs normally only in the bone marrow. The vascular system of the bone marrow is closed; that is, the walls of the vessels are not fenestrated to allow the passage of blood into the tissue spaces. The circulation of the bone marrow may be described as sinusoidal. the capillaries being dilated at intervals into what are known as "sinusoids" of comparatively large diameter. These sinusoids may collapse, it is believed, and have the appearance of collapsed capillaries. The sinusoids may also be removed from the circulation by the collapse of the capillaries on each side of them. Thus we have the possibility of a reservoir removed from the blood stream. The significance of this will be referred to later.

There is difference of opinion concerning the early stages of erythrocyte formation. Maximow, in 1910, suggested that the ultimate origin of erythrocytes was extravascular. He believed that the red cells were derived from a stem cell, the haemocytoblast, which passed through the endothelial lining of the sinusoids as a megaloblast and developed further within the vessel. Evidence has been brought forward by Doan, Cunningham, Sabin, and other workers, that the cells of the endothelial lining of the capillaries of the bone marrow are capable of producing red blood cells. Studies were made in avian, mammalian, and human marrows. The endothelial cells enlarge and undergo division. If the equator of the spindle is perpendicular to the wall of the vessel, two endothelial cells result; if the equator of the spindle is parallel to the wall, the cell next to the wall is an endothelial cell, and that towards the lumen is a megaloblast. The megaloblast is the earliest stage of the red blood cell and is characterized by a large vesicular nucleus, scanty chromatin, large numbers of mitachondria (rod and cocooid forms), little haemoglobin, and much reticulation. The next stages are the early and late erythroblasts; these are distinguished by being the largest stages; they contain a little more haemoglobin, and the mitachondria are grouped about the nucleus. The next stage is the normoblast, which is smaller, the size of an adult erythrocyte, and contains a nucleus and a few mitachondria, the haemoglobin content being complete. The nucleus is then either extruded or absorbed and the resultant form is called the reticulocyte, which is characterized by. having a basophilic network in the cytoplasm but no nucleus. The reticulation disappears and the form is then the adult erythrocyte. This development occurs in the sinusoids, which are closed from the circulation. When the cells are mature the capillaries leading to the sinus become patent and the mature cells are washed into the blood stream.

It is believed that the normal adult marrow does not draw upon the endothelium and megaloblasts for its supply of erythrocytes, but that the normal supply is obtained by division of early and late erythroblasts. In severe anaemias, however, the pattern is reverted in some degree to the megaloblasts and endothelium. While the normal red cell formation in the adult occurs only in the bone marrow, it is believed by some that under severe conditions of anaemia, erythropoietic power may be assumed by spleen and liver, in which organs erythrocytes are produced during embryonic development.

Several factors influence the formation of erythrocytes in the adult.

1. Effect of Haemolytic and Haemorrhage Anaemias.

The effect on the formation of erythrocytes by these two types of anaemias is somewhat different. Price-Jones, in 1910. produced haemolytic anaemia by injecting phenylhydrazin, which destroyed 40-50 per cent. of the red cells by producing haemolysis. This worker found a change in the bone marrow and blood pictures, the marrow contained many megaloblasts, and immature cells were liberated into the blood stream. A delay in the commencement of regeneration was noticed and attributed to the toxic effect of the phenylhydrazin on the bone marrow. Bunting has studied the effects of injection of saponin and ricin; it was found that immature cells appeared in the blood stream, such as macrocytes, which were derived from megaloblasts directly without passing through the intermediate stages. Thus haemolytic agents have a toxic effect upon the bone marrow as well as the effect of breaking down the red corpuscles.

The effect of haemorrhage anaemia has been studied by Price-Jones. Blood was removed by haemorrhage so that a loss of 54-76 per cent. of the oxygen capacity of the blood occurred. It was found that the normal formation of erythrocytes was not interfered with, but was stimulated; more early stages were produced but a greater number of these remained in the marrow and matured. The recovery process is begun in this type of anaemia earlier than in haemolytic anaemia, but is not completed as soon. This is probably due to the fact that the haemoglobin liberated by haemolysis is broken down and worked over and reutilized for blood formation, whereas in haemorrhage anaemia the building stones for haemoglobin must be obtained from the foodstuffs, which process in all probability requires a longer time.

2. Effect of Altitude and Changes in the Oxygen Tension of the Air.

It was first shown by Bert in 1882 and Viault in 1890 that the oxygen capacity of men and animals in high altitudes is increased over that at lower levels. These changes were observed in expeditions to Pike's Peak and the Andes in Peru more recently. All investigators agree that there is a definite increase in the red cells in high altitudes. This is believed to be an emergency measure at first, brought about by a concentration of the plasma volume or a contraction of the spleen; but is later due to increased action of bone marrow.

It is believed that the changes described above which occur in high altitudes are caused by an oxygen want due to a decrease in the partial pressure of oxygen in the respired air. Experimental work concerning the effect of decreased partial pressure of oxygen has been carried on. Campbell has placed monkeys, rabbits, rats and mice in chambers for 33 days in which the pressure was lowered to correspond to that found at an altitude of 33,000 feet. He found an increase in both red cells and haemoglobin. Schauman and Rosenquist have confirmed Campbell's results. Dallwig, Kolls and Loewenhart, in a series of experiments on rabbits,

dogs, and white rats, have found that a decrease in the oxygen of the inspired air, brought about by decreasing the oxygen concentration at atmospheric pressure, or by decreasing the atmospheric pressure, causes an extensive hyperplasia in the bone marrow and an increase in erythrocytes and the haemoglobin. Jordan and Speidel, in 1924, studied the seasonal variation in the erythrocyte in frogs. They found that during the summer, when the frog's metabolism is at a higher level, there is a greater number of red cells than during the winter, when the metabolism of the frog is at a lower level. Then they accelerated the metabolism of frogs by injecting thyroid extract. This produced an increase in the number of red cells. They conclude that probably an increase in the concentration of carbon dioxide produces an increase in the rate of erythropoiesis, suggesting that the acid properties of carbon dioxide tend to decrease the amount of oxygen which is fixed.

This alteration in the red cell count with changes in the oxygen supply indicates an effective regulating mechanism which protects the organism against an oxygen shortage, by increasing the amount of transporting medium when the supply of oxygen is reduced, so that the same amount of oxygen may be made available per unit time. It is interesting to consider that in the sinusoids, referred to above, which are cut off from the circulation, we have a condition which is apparently conducive to the formation of red cells, that is, reduced oxygen tension.

3. The Effect of Diet.

Foodstuffs: In connection with the effect of foodstuffs on red cell formation, little was known before Whipple and Robbscheit-Robbins began a systematic study of the problem. Some workers were of the opinion that some vitamin was concerned with their formation, one group asserting that Vitamin A was intimately related to red cell formation; however, their results are not conclusive and their experimental animals were not in the best of health. In a series of very exact experiments Whipple and Robbscheit-Robbins studied the effect of various foodstuffs upon red cell and haemoglobin formation. Their findings are summarized as follows:

Milk and Milk Products: Milk has no effect at all upon erythrocyte formation, Cream has a slight favorable effect. Butter and cheese have a slightly more favorable effect.

Vegetables: Spinach, beet greens, and lettuce were found to be only moderately good as far as increasing blood formation, while asparagus, carrots, celery and brussel sprouts are even less effective. From the work of Whipple and Robbscheit-Robbins it would seem that the efficacy of vegetables in aiding blood formation has been overestimated.

Fruits: Apricots and peaches are the most effective fruits for blood regeneration, 200 grams producing an output of 40-50 grams of haemoglobin per two week period, when aided by the basal diet. Prunes are slightly less favorable; apples, raisins and grapes slightly less again.

Fish: Fish muscle as well as fish liver have been found to be only slightly effective in blood formation.

Muscle: Muscle tissue both smooth and striated is very effective in red cell formation, smooth muscle being more effective than striated. Chicken gizzard, heart muscle, cattle stomach and cattle muscle are potent in the order named.

Brain and Pancreas: Brain and pancreas are only slightly effective, pancreas being better than brain.

Spleen: Whipple and Robbscheit-Robbins have found that spleen fed to dogs has a fairly good effect upon blood formation. They find a great variation, however, and suggest that it may be due to differences in the amount of haemoglobin destruction in the slaughtered

animals with resulting differences in the amount of haemoglobin building materials in the spleen.

Liver and Kidney: Liver is the most effective foodstuff for blood formation in an anaemic dog, kidney being slightly less effective.

Mineral Salts.—*Iron*: Much work has been done on the effect of iron on blood formation ever since Menghini demonstrated in 1747 that iron was present in blood. Iron has been used extensively in treatment of various disorders of blood formation, many different forms have been tried, organic and inorganic, ferro- and ferri-salts, soluble and insoluble, and more recently the so-called active magnetic form and the inactive non-magnetic form.

The literature is very confusing upon the question of the effectiveness of iron. Some workers suggest that iron acts as a building stone for haemoglobin and others suggest that iron acts as an irritant to the bone marrow to stimulate it to greater activity. There are a few facts, however, which seem to be definitely proven. Williamson and Ets, and Whipple and Robbscheit-Robbins have found that ingestion of iron has little effect upon recovery from anaemia of short duration; however, on administration of iron to a dog suffering from anaemia of long duration beneficial results have been observed; there also seems to be a maximum dose above which level no further effects are produced. It has also been found that the combination of liver or kidney plus iron produces a very marked effect upon blood regeneration in anaemic dogs, much more than that of liver or kidney alone. This would indicate that it is not alone the iron content of liver which is responsible for its very marked effectiveness.

Arsenic: Small doses of arsenic apparently have no effect upon blood formation, but large doses appear to produce a haemolytic anaemia which, of course, leads to active regeneration.

Copper: Waddel, Steenbock, and others found that no recovery occurred when iron alone was added to the milk diet in nutritional anaemia, but when extracts and ashes of cabbage, cornmeal and animl origin were added, signs of recovery appeared. Further investigation revealed that copper was the element responsible in the extracts and ashes. They suggested that copper acted as a catalyst, and did not enter into the molecule itself. This has been confirmed by others.

Pernicious Anaemia.

The blood picture of pernicious anaemia shows a reduced red blood cell count, lowered haemoglobin content, and the presence in the blood stream of immature red cells and of adult red cells which are irregular in form and size. The bone marrow presents changes—it is hyperplastic, with many megaloblasts, indicating a return to the embryonic type of blood formation.

Minot and Murphy in 1926 discovered that feeding of large quantities of liver cured pernicious anaemia. Attempts were made to extract the potent substance. Conn, Minot, Alles and Salter have determined that the potent material in liver producing a cure for pernicious anaemia is either a polypeptide or a nitrogenous base. Following the administration of liver or liver extract, there is a sharp rise in the number of reticulocytes in the blood occurring about nine days after the first administration. This indicates a recovery occurring in the bone marrow with the effect that more mature red cell forms are liberated into the blood stream.

Some very interesting experiments were carried on by Castle in connection with pernicious anaemia. He fed a beef meal to a normal person, and then removed the contents of that person's stomach after a short time of digestion and refed this material to a pernicious anaemia patient. He obtained a recovery in the majority of

cases. Beef digested by means of a pepsin solution did not produce a cure. It has been suggested that the achylia which is present in all cases of pernicious anaemia is the primary cause of the disease, there being some product of digestion which is not produced in pernicious anaemia patients, which product has the same effect as the substance in liver extract.

Surgical Tuberculosis of the Kidney.

By H. R. Brillinger, B.A., 3T1.

Renal Tuberculosis has come into prominence in recent years with the more accurate and frequent analysis of the urine. In the past it was more often unrecognized and it was usually at the autopsy table that its presence was discovered. Chambers, Morris and Tilden Brown found 2.59 per cent. of Renal Tuberculosis in 5,338 autopsies.

This is a disease found mostly between the ages of 15 and 40, according to Boyd. Davis and Falci point out its comparative rarity in young children and aged individuals.

There is some discussion as to which kidney is the more frequently involved. But Wilson points out the uselessness of such quibbling, as one side is just as often affected as the other.

Many men have shown the incidence of other tuberculous lesions accompanying that of the kidney. Chief among these are Braasch and Sholl and Young and Davis, who found Pulmonary Tuberculosis in 28 per cent. of the cases, and Davis, who found bone and joint Tuberculosis in 6 or 7 per cent. of cases.

Mode of Infection.

The portal of entry, however, is often very small and impossible to find. Three modes of transmission to the kidney are possible: 1, by the blood; 2, by lymphatics; 3, by regurgitation from the bladder. This latter, however, is no longer believed. In by far the greater number of cases the infection reaches the kidney through the blood stream. Young and Davis, however, point out that in a few cases in males the infection may ascend the ureter through the lymphatics from previously involved genital organs. Others claim that the kidney is always the first organ to be infected and that any lesions of the lower urinary or genital tract are secondary thereto.

Pathology.

This is a very much disputed field of research. Medlar claims that the infection is haematogeneous, that both kidneys must be showered with the tubercle bacilli, and that therefore Surgical Tuberculosis of the Kidney must necessarily be primarily bilateral. In examining thousands of serial sections of many cases he found both kidneys involved in every case, but the lesions of the presumably healthy kidney were often quite invisible to the naked eye. Moreover, in these kidneys, he points to minute areas of fibrosis as evidence of the healing of these microscopic lesions. His contention is that it is only the lesions which, for some reason or other, progress to a greater size and last over a longer time that are incapable of healing. He found 75 per cent. of lesions in cortex, 11 per cent. in medulla, and 13 per cent. in both. The cortical lesions are the microscopic ones, which have a strong tendency to heal. The medullary and cortico-medullary lesions, however, which predominate in the region of the arcuate vessels, tend to grow and produce macroscopic involvement.

Opposed to Medlar are the great majority of observers, who have reached the conculsion that Renal Tuberculosis is always at the beginning a unilateral disease. The fact

that complete restoration to health follows nephrectomy in so many cases is an important reason for this conclusion. In correlating this unilateral involvement with the haematogeneous mode of infection, Crompton explains that there is probably a minute bolus of bacilli which must lodge in one kidney or the other. Moreover, Wildbolz points out that the tuberculous areas found by Medlar in the kidneys of bodies that had died of pulmonary tuberculosis were often a manifestation of local miliary tuberculosis, local miliary metastases from pulmonary tuberculosis, or there were signs of fibrotic tuberculosis of the kidney.

Boyd classifies Renal Tuberculosis into two groups: (1) Acute or Miliary, for which surgical intervention is impossible, and (2) Chronic or ulcerative, which is the surgical type. The site of the initial lesion is either in the boundary zone at the base of a pyramid, or in the apex of a papilla as it projects into the pelvis. A miliary tubercle composed of endothelial cells, surrounded by a zone of lymphocytes, is formed. The usual necrosis occurs, and the focus may ulcerate into the pelvis, with early infection of the ureter. A retrograde process also commences and and ascends up the lymphatics to the cortex and even to the capsule. The cut surface of one of these kidneys shows: (1) caseous yellow tuberculous masses, notably at the base of the pyramids or at one or both poles; (2) cavities of varying size with rough ragged walls, containing thick, creamy pus, without smell, and sterile in culture; (3) yellowish lines of infection which lead up to clusters of tubercles in the cortex; (4) often extensive ulceration and dilatation of the pelvis with destruction of the papillae; (5) a thickening and dilatation of the ureter, although in some cases there may be a tuberculous stricture.

Wildbolz classifies chronic tuberculosis of the kidney into: (1) Nodular form, in which there is no cavity formation, the tubercles becoming caseous without breaking down; (2) Fibrotic or indurative form, in which both cavity and caseation formation are absent, the tubercles showing an increased tendency to encapsulation; (3) Tuberculous nephritis, in which there is no cavity, caseous, or tubercle formation. As well as the well known (4) Caseo-cavernous type. It is the last-named which is probably the most common.

Complications of Renal Tuberculosis.

The first symptoms complained of are those of a complication namely, tuberculous involvement of the bladder. This appears first as areas of inflammation, going on to bullous formation and later the characteristic shallow serpiginous ulceration, which tends to heal after removal of the offending kidney. Later true tubercles develop and there is no healing after removal of the offending kidney

Before the bladder is involved the ureter is usually affected. This may occur in a number of ways, but a common one is that of ureteral obstruction with a consequent hydronephosis, or pyonephrosis. Secondary infection with common organisms may be a complication and may be due to instrumentation or arise spontaneously. The disease may spread to the capsule with a complicating perinephric inflammation and abscess formation.

Another condition often accompanying renal tuberculosis is the presence of renal calculi. It has not been definitely worked out whether there is any relation between the two, but mention has been made in an article by Kretschmer of a case in which renal calculi of the opposite side disappeared after extirpation of a tuberculous kidney.

The most common condition in males, however, following renal tuberculosis, is involvement of the genital tract. Young and Davis found this complication in 134 out of 205 cases, while Crompton quotes its

occurrence as 70 per cent. of all male cases. The spread is usually by the prostrate and seminal vesicles, with the epididymis last. The last may be first, however, in some cases, and if so it indicates a transmission by blood stream.

Symptoms.

Surgical Tuberculosis is of itself a symptomless disease until the late stages. In fact it is not until the bladder becomes involved that symptoms appear at all. It is known that tubercle bacilli may be excreted by the kidney for a long time before the bladder is affected. Hence patients with symptoms are long standing and relatively advanced cases.

The cardinal symptoms are frequency, burning, and pain. Young and Davis found pain in the kidney as the first symptom in only 44 out of 205 cases. Persson found bladder irritation as the first symptom in 74 per cent. of his cases, hematuria in 5.5 per cent., and renal pain in 18.5 per cent.

Hematuria is often an important symptom, for this occurs also in malignancy and obstruction. The difference is that in malignancy the bleeding precedes the frequency; in obstruction there is frequency followed by very late bleeding.

Other symptoms are loss of weight, chills, fevers, night sweats, physical and mental anguish, and loss of sleep. Davis points out that the bladder symptoms are progressive—frequency progressing to false incontinence — pain, constant and worse on voiding—urgency progressing to tenesmus. There may be periods of renal colic, followed by the passage of blood clots. When hydronephrosis is superimposed there is often a noticeable tumor.

Death is eventually from accompanying tuberculosis lesions or uremia.

Diagnosis.

There is often the history of tuberculosis in the other members of the family. Often also symptoms may be elicited of pre-existing tuberculous lesions in the patient. A general physical examination may reveal pulmonary, bone, gland, or skin tuberculosis. Fistula in ano, persistent fistulae in scrotum or urethra apart from urinary obstruction may indicate tuberculosis. Tenderness in kidney region on pressure over bladder may be found. The testes, epididymis, prostrate, and seminal vesicles should be palpated for irregularities, nodules or indurations.

One of the chief methods of diagnosis, however, is that of urinalysis. R. I. Harris, while at the Hospital for Sick Children, drew considerable attention to this phase of the work by his investigation of urine from a large number of patients suffering from bone and joint tuberculosis. By microscopic examination, and especially by guinea pig inoculation, he showed the occurrence of bacilluria to be far in excess of that commonly thought to occur among patients with surgical tuberculosis. He found a positive urine in 37 per cent. of adults and 13.8 per cent. of children. The renal origin of the tubercle bacilli in the urine was definitely demonstrated in over half of these cases. Moreover pus practically always accompanied these bacilli. This is a sign of inammatory foci in the kidney, i.e., foci of tuberculosis. While many of these cases showed no renal symptoms at the outset, they eventually developed. On the other hand, patients may have tuberculosis of the kidney without positive urine as the lesions may be cortical and not communicate with the pelvis.

A still further method of diagnosis is by cystoscopy. The typical shallow serpiginous tuberculous ulcer may be seen surrounded by a halo of inflammation. The most common location is on the trigone and in relation to the ureter of the affected side. Yellow patches may be noted even before ulceration. Tubercles may be seen in the late stage. In addition there may be a diffuse and apparently acute cystitis

with congestion and edema. If the ureter is extensively involved and shortened, it may pull up the corresponding corner of the trigone and transmit to it the respiratory movements of the diaphragm. In the late stages, the bladder may be greatly contracted with extensive ulceration, edema, masses of mucus, pus, blood-clots, slough and granulation tissue.

To discover which kidney is affected, catheterization of ureters may be undertaken. As a last resort, and only in doubtful cases, the pyelogram may be used. With this, a tip of one or more of the calyces may be seen replaced by an irregular moth-eaten cavity in which no trace of the normal umbilication can be made out.

Differential functional tests are not so important in the diagnosis of early renal tuberculosis as they are in the later stages. Their chief function is in comparing the states of the two kidneys.

Treatment.

The consensus of opinion is that for uncomplicated, unilateral, chronic renal tuberculosis the only hope of cure is in nephrectomy. But this must not be lightly undertaken until a thorough investigation of the patient has been made, by all the means possible, to satisfy the surgeon on three points, namely:

(1) Is the opposite kidney involved, and if so, to what extent?

(2) Are any additional lesions present in the urogenital tract? and

(3) Are there active foci of tuberculosis elsewhere in the body?

If the opposite kidney is infected, Wildbolz and Kratchmer advise against operation. The incidence of death within one or two years of exacerbation of the disease in the other organ, following nephrectomy of the diseased one, is too great to run the risk, no matter how slight the infection of the good side is deemed to be. Even in a large majority of the cases in which the other side is declared to be free from disease, it has subsequently made its appearance with a fatal result. The apparent cases of healing of the opposite kidney following nephrectomy are declared by Wildbolz to be founded upon the false evidence of positive guinea-pig innoculation with urine secreted from that side which might easily have been a reflex sample from the bladder. Kretchmer lays great stress on the pyelogram investigation in these cases. Both emphasize the fact that there is no hurry in making a decision regarding treatment as the disease is chronic and investigation covering weeks is better than taking out a kidney when the other one is also involved, and causing premature death by throwing extra work on the other already damaged kidney. Davis, however, feels that "where the affected kidney is the site of a severe and advanced lesion, and the function of the opposite kidney is normal, the presence of a little pus or a few bacilli demonstrated with difficulty should probably not deprive the patient of a chance of clinical cure which he will have as a result of nephrectomy." This latter opinion is also held by Wilson.

Active foci of tuberculosis elsewhere in the body does not necessarily contra-indicate nephrectomy. It depends on their extent and the state of the patient. They may also influence the manner in which the operation is performed. For instance, a patient with pulmonary tuberculosis complicating an active old unilateral renal lesion might be greatly benefited by nephrectomy, but it would have to be carried out under spinal anaesthesia.

The choice of operation is that of a lumbar extra-peritoneal nephrectomy. Extensive resection of the fatty capsule is unnecessary except for perinephric abscess. Care should be taken to avoid tearing the kidney and spilling the tuberculous pus in the wound, or squeezing the kidney so as to drive tuberculous bacilli into the blood stream. There is grave danger of a miliary tuberculosis following this

operation, or of death from tuberculous meningitis. The ureter should be clamped, tied, and divided with a cautery. A small quantity of carbolic acid injected into it destroys the mucosa and tends to produce fibrous healing, according to Young. The ureter may then be fastened into the end of a rubber drainage tube which protrudes from the lower end of the wound. It may be brought out near the surface and attached to the fascia or skin edges. This is not advisable, however, as there is a grave danger of a persisting sinus. Or, complete ureterectomy may be done. This is not advisable, as it makes the operation much longer and more shocking since it necessitates a laparotomy. The best way is to simply drop the ureter back into the wound without drainage. For the closure of the wound no drainage is needed if the kidney is carefully removed without contamination. If there is slight soiling, a small tube removed in two to four days may be used. Avoid gauze drains. Burns advocates through-and-through silver wire sutures to minimize foreign material in the wound.

The danger is of tuberculous infection of the wound. There may be apparent healing for two or three weeks, followed by separation of the edges, with the walls covered with a grayish membrane, a thin seropurulent discharge, and no healthy graulations. With this condition, healing is very slow—from 3 to 12 months. Treatment is by irrigations, applications of stimulating substances, such as iodoform, or Balsam of Peru, and exposure to sunlight, or ultra-violet rays.

All surgical treatment should be supplemented both before and after operation by the usual constitutional treatment for tuberculosis,—rest, proper diet, and heliotherapy. Crance advocates ultra-violet radiation for those cases of inoperable bilateral renal involvement. Certainly it is worth trying.

For the bladder complications, instillations of argyrol, mercurochrome. or gomenol may be tried. Here also, Rosving's method of injecting carbolic acid up to 6 per cent. may be used.

Prognosis.

The prognosis of unilateral renal tuberculosis without operation is bad, the other side commonly becoming infected with ultimate death. On the other hand, nephrectomy holds out a splendid chance of recovery. Wildbolz claims a 59 per cent. cure ten years after operation. Rafin claims a 44.5 per cent. cure. Over against this may be placed the operative mortality of nephrectomy for tuberculosis as 7 per cent. for Kummel. 7.3 per cent. for Persson, 2.9 per cent. for Braasch, 2.4 per cent. for Wildbolz, and .89 per cent. for Young and Davis. Of course it must be remembered that in order to keep down the mortality the cases must be thoroughly investigated before operation is undertaken.

Summary.

Much work remains to be done in order to clear up the difficulties which this disease presents. The only curative treatment for Surgical Tuberculosis of the Kidney is Nephrectomy in the early stages while it is yet Unilateral. It must always be kept in mind, however, that the disease is chronic and should in every case be subjected to the most thorough investigation before deciding upon operative treatment.

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Some Aspects of the Lymphatic System.

By Douglas Telford, B.A., 3T3.

Introduction.

The lymphatic system is far less conspicuous than the blood vascular but is by no means less important. It forms a closed system and consists of the tissue fluid or lymph, a complex network of capillaries receiving this fluid from the various organs and tissues, an elaborate system of collecting tubules, two large ducts, the thoracic and right lymphatic, which open into the junction of the subclavian and internal jugular veins on the left and right side respectively, and lymph glands or nodes which are interjected in the course of the vessels.

Development.

The lymphatics arise as local transformations of the mesoderm into endothelial islands, such as are represented by the islands of lymph sacs which appear beside the sciatics and renals and at the junction of the subclavian and jugular veins. These sacs form permanent connections with the veins in their neighborhood and send out lymphatic vessels which spread along lines more or less corresponding to the course of embryonic blood vessels. Connections are established between the different sacs An outgrowth of the left jugular, for example, anastamoses with a similar outgrowth of the cisterna chyli to form the thoracic duct.

The first lymph nodes arise in the axillary, iliac and maxillary regions about the third month of development. Soon others appear in the vicinity and more peripherally producing the superficial lymphatic groups. The deep groups appear in the region of the jugular and mesenteric sacs, which have been mentioned above. These sacs are converted into ncdes by the invasion into their substance of connective tissue bridges.

Structure.

The lymphatic capillaries are found in practically all body tissues. They are finely meshed tubes consisting of a single layer of endothelial cells. They anastamose freely at all times, and often end blindly as cul-de-sacs which are common in the intestinal villi.

The larger vessels are exceedingly delicate and are composed of three coats; an internal, of a thin transparent slightly elastic layer of elongated endothelial cells supported on an elastic membrane; a middle coat of smooth muscular and fine elastic fibres disposed in a transverse direction; and an external coat of connective tissue intermingled with smooth muscle fibres longitudinally disposed. These muscle fibres are innervated by fine non-medullated nerve fibres which presumably place the vessels under the control of the vasomotor center. Little is known, however, about the conditions affecting expansion and contraction, so nothing definite can be concluded. The vessels contain many valves, especially abundant near the lymph glands. These valves are indicated on the surface by constrictions which give the vessels a knotted appearance.

The lymph nodes or glands, as they are more popularly called, are interjected in the course of the larger vessels. They are round or renniform structures varying in length from a few mm. to a few cm. A lymph gland consists of a capsule of fibrous and muscular tissue which projects into the interior of the gland as a system of supporting trabeculae dividing the gland into communicating sinuses, a quantity of lymphoid tissue suspended in these spaces in the form of nodules at the periphery and cords at the centre, a free supply of arteries and veins which are supported in the trabeculae,

the afferent and efferent vessels which bring the lymph to and from the gland respectively, and nerves which pass along the arteries to be chiefly distributed to them and the muscular tissue of the gland.

Composition of Lymph.

Lymph is not identical with blood plasma nor with intracellular fluid, but all three are similar. It is a transparent colorless fluid of sp. gr. of 1.015. If collected from the thoracic duct subsequent to the ingestion of fats, however, it has a milky appearance due to the absorption of the fats by the lymphatic lacteals of the intestine. It contains the three blood proteins, the extractives as urea, cholesterol, sugar, etc., and inorganic salts. The last mentioned occur in the same proportion as in the plasma, while the proteins likely due to their indiffusible colloidal nature occur in less concentration. Leucocytes of the small lymphocyte variety are numerous while red blood cells are scarce, and platelets absent. The ordinary constituents necessary for clotting as fibrinogen, prothrombin and calcium salts are also found.

Lymph Production.

Lymph or tissue fluid may be looked upon as part of the plasma, which exudes through the capillary walls to fill the intercellular spaces of practically all tissues. Many physiologists have thought that the exudation of the lymph through the capillary walls is an active secreting process on the part of the endothelial cells of the capillary membrane. The popular opinion now is that the capillary membranes are passive and act only as filters of varying permeability and that the factors which are responsible for the passage of the lymph are filtration, diffusion and osmosis. The first of these factors causes a production of lymph in any capillary area in which the blood in the vessels is at a greater pressure than the fluid in the extravascular spaces. This process of simple filtration is the most important in the intestine and liver, where the capillaries are comparatively permeable. In the limbs and general connective tissues the capillaries not only permit of filtration under certain processes but also allow the passage of water and dissolved substances by the processes of diffusion and osmosis. Thus a gland in activity uses up oxygen, calcium or other dissolved substances, and immediately causes depletion of these substances in the surrounding lymph. This activity disturbs the equilibrium and a flow of the dissolved oxygen, calcium, etc. takes place until equal concentrations exist in the cellular fluid, lymph and plasma. Equilibrium is again upset during activity when CO_2 and other waste products are formed in the tissue cells. Here again through the intermediation of the lymph equal concentrations of the waste products are brought about in the tissue cells and blood plasma.

If dextrose is injected into the circulation, the osmotic equilibrium between blood and lymph is disturbed and returns only after water has passed from lymph to plasma and from tissue cells to lymph. This is the process which takes place following digestion when osmotically active substances are increased in the blood. This same process may be reversed with a resulting increase in the volume of lymph. In muscular activity, for example, large molecules of protein or carbohydrate are broken down into smaller ones, thus increasing the osmotic pressure within the tissue cells, and a passage of water occurs from lymph to cells and from blood to lymph.

Under certain pathological conditions the production of lymph is greatly increased and the result is often the collection of large amounts of lymph in the affected tissues giving the condition of oedema. A deficient amount of oxygen due to arterial thrombosis, destruction of tissues as in freezing or scalding, or the injection of certain

poisons have the special action of increasing the permeability of the capillary membrane. Some of the lymphagogues (substances increasing the production of lymph) as peptone or extracts of intestine or liver act in the same way and have their effect in their poisonous action on the vascular walls.

Circulation of the Lymph.

The lymph flows from the extravascular spaces through the lymphatic capillary walls and along the capillaries and larger vessels to the nodes. It enters the peripheral sinuses of the node by the afferent vessels, percolates through the sinuses by passing between the recticulo-endothelial and lymphoid tissue there and leaves by the efferent vessels at the hilus of the gland. These last named vessels soon unite to form the thoracic or right lymphatic duct which conduct the flow to the blood stream.

The flow is maintained in this direction by several factors, the chief of which is the difference in pressure between the lower central and higher peripheral pressures. At the openings of the large trunks into the junction of the subclavian and internal jugular veins the pressure is very low, often zero and sometimes negative. At the other extremity of the system, that is the tissue spaces, the reverse condition exists. The pressure is high and is kept so by the blood within the adjacent capillaries. The lymph in the tissue spaces in turn maintains the pressure in the lymphatic vessels since the walls of the latter are permeable to the tissue fluid. There is then a gradient ranging from 10-40 mm. of Hg. in the blood capillaries to only a few mm. of Hg. in the lymphatic vessels.

The circulation of the lymph is in addition aided by many accessory factors. In some animals, there are genuine lymph hearts in the course of the vessels. In the mammals no such structures are present, but muscle fibres, circularly and obliquely arranged, surround the larger lymphatic channels and may or may not assist the flow of lymph. The receptaculum chyli is believed by some to undergo contractions and in this respect to resemble to some extent the pulsatile beats of the structure found in some of the lower animals.

The peristalsic and rhythmical movements of the intestinal musculature and the independent movements of the villi act like a pump and accelerate the flow of lymph along the lacteals. A similar influence is exerted by the contraction of the skeletal muscles. The contraction of the muscle fibres forces the lymph onward. Relaxation of these same fibres is prevented from having the reverse effect because of the presence of valves. The fact that the flow of lymph from resting muscle is slow, while that from active muscle is considerably greater, is consistent with the above facts.

Still another factor influencing the flow of lymph is that of respiratory movements of the thorax. At each inspiration the pressure in the thorax is diminished. This increased negative pressure by lowering the intra-thoracic pressure on the thoracic duct aspirates the lymph from the abdominal portion of the duct.

All the just mentioned factors maintain a flow of lymph along the large ducts at a speed of perhaps only 4 mm. per sec. and with a volume ranging anywhere from 50 to 100 c.c. per hour. depending upon the muscular and metabolic activity of the body.

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